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SKIN BLEACHING COMPOSITION

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SKIN BLEACHING COMPOSITIONAbstract of the Disclosure

A synergistic skin-bleaching composition for use by topical application has been found which comprises a mixture of a bleaching agent, a skin irritant-exfoliating agent and an anti-inflammatory agent formulated in a pharmaceutically-cosmetically acceptable vehicle. The composition comprising 2% hydroquinone, 0.05% retinoic acid and either 0.025% dexamethasone or fluorometholone was particularly effective.

Background of the Invention

1) Field of the Invention: This invention relates to a new synergistic skin-bleaching composition for use by topical application.

2) Description of the Prior Art: So-called compositions for the bleaching of skin have been known for many years, if not centuries. The prior art contains many references to the use of hydroquinone and its derivatives as agents in bleaching creams, etc., the most pertinent of which are:

a) U. S. Patent No. 3,060,097, issued October 23, 1962 to a skin-bleaching composition comprising sodium hypochlorite, hydroquinone monobenzyl ether and a "penetrant". Three British Patents No.'s 763,029, 855,431 and 965,869 issued to the same inventor on similar compositions.

b) French Patent No. 1,513,395, issued January 8, 1968 to a skin-bleaching composition comprising hydroquinone monobenzyl ether or a derivative thereof in combination with tyrothricin or a derivative thereof.

c) French Patent No. 1,270,854, issued July 24, 1961 to

1 a skin-bleaching composition comprising hydroquinone benzyl
2 ether (1'ether of benzylhydroquinone) and an anti-oxidant.
3 The product may be formulated to contain vitamins, amino
4 acids, cholesterol, etc.

5 d) United States Patents No.'s 2,274,725 (March 26, 1942),
6 2,376,884 (May 29, 1945) and 2,377,188 (May 29, 1945) are to sun-
7 screen preparations comprising hydroquinone as the active sun-
8 filter agent. These preparations are stabilized by the addition
9 of certain anti-oxidants.

10 e) Zachr. Haut-Geschl.-Krank. 42, 17: 711-716 reports
11 studies of bleaching the skin using hydroquinone monobenzyl
12 ether. When a subject was found to have sensitive skin, 5%
13 hydroquinone monobenzyl ether and 4% prednisolone was used to
14 prevent or control the contact dermatitis produced by the hydro-
15 quinone monobenzyl ether. No mention is made of an improved
16 bleaching effect when the preparation contained prednisolone.

17 f) Some other articles reporting on skin-bleaching by the
18 use of hydroquinone or its derivatives are:

- 19 1. Archives of Dermatology, 84, No. 1, 131-134 (July
20 1961).
- 21 2. Clinical Medicine, 70, No. 6, 1111-1114 (June 1963).
- 22 3. Clinical Medicine, 72, No. 3, 87-88 (March 1966).
- 23 4. Postgraduate Medicine, 37, No. 2, 198-201 (February
24 1965).
- 25 5. J. Investigative Medicine, 18, 119-135 (1952).
- 26 6. J. Am. Medical Assoc., 152, No. 7, 577-582 (June
27 13, 1953).
- 28 7. Dermatologica, 134, 127-128 (1967).
- 29 8. Archives of Dermatology, 93, No. 5, 589-600 (May
30 1966).

1 The above cited art constitutes but a small portion of the
2 prior art but is representative of that deemed most pertinent.
3 None of the above teaches or anticipates the three component,
4 synergistic compositions of the present invention.

5 Summary of the Invention
6

7 A synergistic skin-bleaching composition for external appli-
8 cation has been found comprising a bleaching agent selected from
9 the group comprising hydroquinone, hydroquinone monomethyl ether,
10 hydroquinone monoethyl ether and hydroquinone monobenzyl ether,
11 a skin irritant-exfoliating agent and an anti-inflammatory cor-
12 ticosteroid.

13 Complete Disclosure

14 It has long been desirable in certain skin disorders or
15 diseases to be able to depigment (bleach) the skin to remove
16 certain disfiguring blemishes generally caused by the deposi-
17 tion of excess quantities of melanin. This hyperpigmentation
18 is generally viewed as cosmetically undesirable or psychologi-
19 ally disabling. Examples of these blemishes would be freckles,
20 sunspot, lentigo, lentigines (liver spots), melasma, contact
21 allergy pigmentation, sunburn pigmentation, post-inflammatory
22 hyperpigmentation due to abrasion, burns, wounds, dermatitis,
23 phototoxic reaction and other similar small, fixed pigmented
24 lesions. Likewise, it is also desirable to be able to decolorize
25 normally pigmented skin to generally increase "fairness" of
26 appearance and to blend hypopigmented areas into surrounding
27 bleached skin. This is particularly so in the treatment of
28 negroes, brown-skin people, or generally dark skinned people
29 suffering from vitiligo.
30 It was an object of the present invention to prepare an

1 effective and superior product as compared to those currently
2 on the market or known in the literature.

3 The compounds hydroquinone, hydroquinone monomethyl ether,
4 hydroquinone monobenzyl ether, ammoniated mercury, zinc peroxide,
5 red mercuric oxide, sodium hypochlorite, hydrogen peroxide, mer-
6 curous chloride and bichloride of mercury are all known in the
7 literature as bleaching agents of the skin. Only hydroquinone
8 is recognized as a bleaching agent possessing satisfactory
9 qualities.

10 The object of the present invention has been achieved by the
11 formulation of a superior synergistic skin-bleaching composition
12 for external application which comprises a mixture of a bleaching
13 agent, a skin irritant-exfoliating agent and an anti-inflammatory
14 agent in a pharmaceutically-cosmetically acceptable vehicle.

15 A preferred embodiment of the present invention is a syner-
16 gistic skin-bleaching composition for external application com-
17 prising a bleaching agent selected from the group comprising
18 hydroquinone, hydroquinone monomethyl ether, hydroquinone mono-
19 ethyl ether and hydroquinone monobenzyl ether, a skin irritant-
20 exfoliating agent and an anti-inflammatory corticosteroid for-
21 mulated in a pharmaceutically-cosmetically acceptable vehicle.

22 Another preferred embodiment is a synergistic skin-bleaching
23 composition for external application comprising about 1% to about
24 10% of a bleaching agent selected from the group comprising hydro-
25 quinone, hydroquinone monomethyl ether, hydroquinone monoethyl
26 ether and hydroquinone monobenzyl ether, and about 0.025% to about
27 80% of a skin irritant-exfoliating agent and about 0.01% to about
28 3.0% of an anti-inflammatory corticosteroid formulated in a phar-
29 maceutically-cosmetically acceptable vehicle.

30 Another preferred embodiment is a synergistic skin-bleaching

1 composition for external application comprising about 1% to
2 about 5% of a bleaching agent selected from the group comprising
3 hydroquinone, hydroquinone monomethyl ether, hydroquinone mono-
4 ethyl ether and hydroquinone monobenzyl ether, about 0.025% to
5 about 15% of a skin irritant-exfoliating agent selected from
6 the group comprising unsaturated fatty acids, long chain fatty
7 acid esters or salts thereof, retinoic acid, oleic acid, arachidi-
8 onic acid, polyoxyethylene lauryl or myristyl ethers, alky-
9 amines containing 5 to 16 carbon atoms, salicylic acid and benzoic
10 acid, and about 0.01% to about 3.0% of an anti-inflammatory
11 corticosteroids selected from the group comprising hydrocorti-
12 sone, cortisone, prednisolone, prednisone, dexamethasone, beta-
13 methasone, fluocinolone acetonide, triamcinolone, fluocinolone,
14 triamcinolone acetonide, methylprednisolone, fluorometholone,
15 or an ester thereof when chemically possible, formulated in a
16 pharmaceutically-cosmetically acceptable vehicle.

17 A more preferred embodiment is a synergistic skin-bleaching
18 composition for external application comprising about 1% to about
19 5% of hydroquinone, about 0.020% to about 10% of a skin irritant-
20 exfoliating agent selected from the group comprising retinoic
21 acid, arachidonic acid, oleic acid, linoleic acid, linolenic
22 acid, sodium lauryl sulfate, dioctyl sodium sulfosuccinate,
23 polyoxyethylene lauryl ether, polymyristylene myristyl ether,
24 salicylic acid, benzoic acid, and n-octylamine, and about 0.01% to
25 about 5% of an anti-inflammatory corticosteroid selected from the
26 group comprising dexamethasone, betamethasone, fluocinolone, flu-
27 cinalone, acetonide, triamcinolone, hydrocortisone, triamcinolone,
28 acetonide, fluorometholone, or an ester thereof when chemically possible,
29 formulated in a pharmaceutically-cosmetically acceptable vehicle.

30 A most preferred embodiment is the synergistic skin-bleaching

1 composition for external application comprising about 2% hydro-
2 quinone, about 0.05% retinoic acid and about 0.025% fluocinolone
3 formulated in a pharmaceutically-cosmetically acceptable vehicle.

4 Another most preferred embodiment is the synergistic skin-
5 bleaching composition for external application comprising about
6 2% hydroquinone, about 0.05% retinoic acid and about 0.025%
7 dexamethasone formulated in a pharmaceutically-cosmetically
8 acceptable vehicle.

9 Still another most preferred embodiment is the synergistic
10 skin-bleaching composition for external application comprising
11 about 2% hydroquinone, about 0.05% retinoic acid and about 2.5%
12 hydrocortisone or hydrocortisone acetate ~~formulated in a pharm-~~
13 ceutically-cosmetically acceptable vehicle.

14 A preferred embodiment of the present invention is a method
15 of bleaching human skin by applying to the skin a synergistic
16 skin-bleaching composition which comprises a mixture of a bleaching
17 agent, a skin irritant-exfoliating agent and an anti-inflammatory
18 agent formulated in a pharmaceutically-cosmetically acceptable
19 vehicle.

20 Another preferred embodiment is the method of bleaching
21 human skin wherein the bleaching composition comprises a
22 bleaching agent selected from the group comprising hydroquinone,
23 hydroquinone monomethyl ether, hydroquinone monoethyl ether and
24 hydroquinone monobenzyl ether, a skin irritant-exfoliating agent
25 and an anti-inflammatory corticosteroid formulated in a pharma-
26 ceutically-cosmetically acceptable vehicle.

27 A further preferred embodiment is the method of bleaching
28 human skin wherein the bleaching composition comprises about 1%
29 to about 10% of a bleaching agent selected from the group com-
30 prising hydroquinone, hydroquinone monomethyl ether, hydroquinone

1 monoethyl ether and hydroquinone monobenzyl ether, and about 0.025%
2 to about 30% of a skin irritant-exfoliating agent and 0.01% to about
3 3.0% of an anti-inflammatory corticosteroid formulated in a pharmaceu-
4 cally-cosmetically acceptable vehicle.

5 A more preferred embodiment is the method of bleaching human
6 skin wherein the bleaching composition comprises about 1% to about
7 5% of a bleaching agent selected from the group comprising hydroquinone,
8 hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydro-
9 quinone monobenzyl ether, about 0.025% to about 15% of a skin irri-
10 tant-exfoliating agent selected from the group comprising unsaturated
11 fatty acids, long chain fatty acid esters or salts thereof, retinoic
12 acid, arachidonic acid, polyoxyethylene lauryl or myristyl ethers,
13 oleic acid, ethylenes containing 5 to 16 carbon atoms, salicylic
14 acid and benzoic acid, and about 0.1% to about 3.0% of an anti-
15 inflammatory corticosteroids selected from the group comprising
16 hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone,
17 betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone,
18 triamcinolone acetonide, methylprednisolone, fluorometholone, or an
19 ester thereof when chemically possible, formulated in a pharmaceu-
20 cally-cosmetically acceptable vehicle.

21 Another more preferred embodiment is the method of bleaching
22 human skin wherein the bleaching composition comprises about 1% to
23 about 5% of hydroquinone, about 0.020% to about 10% of a skin irri-
24 tant-exfoliating agent selected from the group comprising retinoic
25 acid, arachidonic acid, linoleic acid, oleic acid, linolenic acid,
26 sodium lauryl sulfate, dioctyl sodium sulfosuccinate, polyoxy-
27 ethylene lauryl ether, polyoxyethylene myristyl ether, salicylic
28 acid, benzoic acid, and n-octylamine, and about 0.01% to about
29 3% of an anti-inflammatory corticosteroid selected from the group
30 comprising dexamethasone, betamethasone, fluocinolone, flucinolone

1 acetonide, triamcinolone, hydrocortisone, triamcinolone acetonide,
2 fluorocortisolone, or an ester thereof when chemically possible,
3 formulated in a pharmaceutically-cosmetically acceptable vehicle.

4 A most preferred embodiment is the method of bleaching
5 human skin wherein the bleaching composition comprises about
6 2% hydroquinone, about 0.05% retinoic acid and about 2.5%
7 hydrocortisone or hydrocortisone acetate formulated in a phar-
8 maceutically-cosmetically acceptable vehicle.

9 A most preferred embodiment is the method of bleaching
10 human skin wherein the bleaching composition comprises about
11 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluoro-
12 methalone formulated in a pharmaceutically-cosmetically acceptable
13 vehicle.

14 Another most preferred embodiment is the method of bleaching
15 human skin wherein the bleaching composition comprises about 2%
16 hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone
17 formulated in a pharmaceutically-cosmetically acceptable vehicle.

18 Hydroquinone, hydroquinone monomethyl ether and hydro-
19 quinone monobenzyl ether are all known in the literature as
20 bleaching agents for lightening of the skin. While there is
21 some question as to the mode of action of these agents and treat-
22 ment is considered an "art" rather than a science, it is generally
23 thought that all of these agents work through the common inter-
24 mediate hydroquinone. Additionally, it is known that hydro-
25 quinone is the least irritating of these hydroquinones, the
26 ethers generally having the reputation of causing various types
27 of dermatitis. It is also known that the ethers are unpredictable
28 in their bleaching effect and sometimes cause a progression of
29 depigmentation after application has been stopped. Hydro-
30 quinone is the agent of choice when a hydroquinone bleaching

agent is desired for these reasons.

A 2% hydroquinone composition is commercially available under the trademarks "Eldoquin" and "Eldopaque" by Paul Elder & Company. Hydroquinone is reported to be the sole active ingredient.

In our hands, it has been found that a preparation containing only 2% hydroquinone is unpredictable and not always effective. Similar results have been reported in the literature (Clinical Medicine, 72, No. 3, 87-88 [March 1966]), wherein 35% of those subjects treated showed excellent results, 5% good, 35% fair and 25% poor.

Subsequent investigations to improve these results were undertaken and it has been unexpectedly found that a composition containing hydroquinone, or a derivative thereof, in combination with a skin irritant-exfoliating agent and an anti-inflammatory, corticosteroid produced good to excellent results in almost all of the subjects so treated. One must consider these results to be a type of synergism inasmuch as these superior results can not be achieved by any of the individual components alone.

The compositions of the present invention are applied according to the following general regimen: In the case of the formulation of example 1, the composition was applied two to three times daily to the areas to be bleached. The composition is preferably applied three times a day for two days, then two times a day till irritation (mild inflammation) can be seen. Depending upon the degree of irritation, the composition is applied once or twice a day till depigmentation occurs. Depigmentation usually begins to occur five to twenty-one days after the initial application. Depigmentation is usually complete within six to ten weeks.

1 In patients with recurrent hyperpigmentation (negroes,
 2 other dark-skinned races, — pigmentation can be maintained
 3 by several applications per week.

4 The results produced by the application of the above com-
 5 position are exceptionally good. In almost 100% of the subjects
 6 so treated, good to excellent depigmentation was obtained. The
 7 results were particularly dramatic in normal negro skin, wherein
 8 the skin was bleached white in the majority of subjects so treated.

9 Generally, similar results can be obtained with any of the
 10 formulations of the present inventions, although the frequency
 11 of application, the time required for depigmentation and the
 12 degree of depigmentation will vary with the components strength,
 13 and pharmaceutical vehicle used.

14 Examples of the Embodiments

15 Example 1

16	Hydroquinone	2%
17	Retinoic Acid	0.05%
18	Fluorometholone	0.625%
19	Fragrance q.s.	
20	Propylene glycol	
21	Ethanol (95%) q.s. ad 100 ml.	

22 Finely pulverize the hydroquinone, retinoic acid and fluoro-
 23 metholone and dissolve in about 80 ml. of the 50:50 mixture of
 24 propylene glycol and ethanol. Add the fragrance and q.s. ad to
 25 100 ml. Mix well and apply to area to be bleached.

26 Example 2

27 Substitution in the formula of Example 1 for the fluoro-

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1 metholone used therein of 0.025% of dexamethasone produces an
2 equivalent formulation.

3 Example 3

4 Hydroquinone 2%

5 Retinoic acid 0.05%

6 Fluorometholone 0.025%

7 Vanishing Cream base q.s. ad 100 gm.

8 Finely pulverize the hydroquinone, retinoic acid and fluoro-
9 metholone. Add a small quantity of the vanishing cream base and
10 mix well to obtain a gritless paste. Add additional vanishing
11 cream base to make 100 gm. of product. Mix well and apply.

12 Example 4

13 Hydroquinone 2%

14 Retinoic acid 0.05%

15 Fluorometholone 0.025%

16 Emollient lotion q.s. ad 100 ml.

17 Finely pulverize the hydroquinone, retinoic acid and fluoro-
18 metholone. Add a small quantity of the emollient lotion to the
19 powder to make a gritless paste. Add sufficient lotion to make
20 100 ml. Mix well and apply.

21 Example 5

22 Hydroquinone 2%

23 Retinoic acid 0.05%

24 Hydrocortisone 2.5%

25 Vanishing cream base q.s. ad 100 gm.

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1 Prepare as in example 3.

2		
3		
4	Hydroquinone	2%
5	n-Octylamine	0.5%
6	Fluorometholone	0.025%
7	Vanishing cream base q.s. ad 100 gm.	

8

9 Finally pulverize the hydroquinone and fluorometholone.

10 Add the n-octylamine and a small quantity of vanishing cream

11 to make a gritless paste. Add sufficient vanishing cream to

12 take 100 gm. Mix well and apply.

13		
14		
15	Hydroquinone	2%
16	Sodium lauryl sulfate	5%
17	Fluorometholone	0.025%
18	Vanishing cream base q.s. ad 100 gm.	

19

20 Prepare as in example 3.

21		
22		
23	Hydroquinone	2%
24	Linoleic acid	50%
25	Fluorometholone	0.025%
26	Propylene glycol	
27	Ethanol (95%) q.s. ad 100 ml.	
28		

29 Prepare as in example 1.

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Example 9

1 Hydroquinone 25
2 Linolenic acid 55%
3 Fluorometholone 0.025%
4 Propylene glycol
5 Ethanol (95%) 52 q.s. ad 100 ml.

6 Prepare as in example 1.

Example 10

11 Hydroquinone 25
12 Arachidonic Acid 10%
13 Fluorometholone 0.025%
14 Propylene glycol
15 Ethanol (95%) 52 q.s. ad 100 ml.

16 Prepare as in example 1.

Example 11

19 Hydroquinone 25
20 Polyoxyethylene lauryl ether 10%
21 Fluorometholone 0.025%
22 Propylene glycol
23 Ethanol (95%) 52 q.s. ad 100 ml.

24 Prepare as in example 1.

Example 12

25 Hydroquinone monobenzyl ether 5%
26 Retinoic acid 0.05%

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1 Fluorometholone 0.025%
2 Vanishing cream base q.s. ad 100 gm.

3
4 Prepare as in example 3.

5 Example 13
6
7 Hydroquinone 5%
8 Retinoic acid 0.35%
9 Fluorometholone 0.05%
10 Vanishing cream base q.s. ad 100 gm.

11
12 Prepare as in example 3.

13
14 The above examples are illustrative of some of the variations
15 in formulation that can be made within the scope of the present
16 invention.

17 To prepare a more elegant or stable product, it may be de-
18 sirable to incorporate fragrances, pigments, preservatives and/or
19 a stabilizer including anti-oxidants, all of which are within the
20 ability of those knowledgeable in the art.

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A synergistic skin-bleaching composition for external application which comprises a mixture of 10% to about 20% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monethyl ether and hydroquinone monobenzyl ether, about 0.02% to about .001% of retinoic acid as a skin irritant-exfoliating agent, and about 0.01% to about 3.0% of an anti-inflammatory corticosteroid, formulated in a pharmaceutically-cosmetically acceptable vehicle.
2. A composition of claim 1 comprising about 1% to about 5% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monomethyl ether and hydroquinone monobenzyl ether, about 0.025% to about .05% of retinoic acid and about 0.01% to about 3.0% of an anti-inflammatory corticosteroid selected from the group comprising hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone, triamcinolone acetonide, methylprednisolone, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.
3. A composition of claim 1 comprising about 1% to about 5% of hydroquinone, about 0.020% to about 10% of retinoic acid as an skin-irritant-exfoliating agent, and about 0.01% to about 3% of an anti-inflammatory corticosteroid selected from the group comprising dexamethasone, betamethasone, flucinolone, flucinolone acetonide, triamcinolone, hydrocortisone, triamcinolone acetonide, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

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4. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluorometholone formulated in a pharmaceutically-cosmetically acceptable vehicle.
5. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone formulated in a pharmaceutically-cosmetically acceptable vehicle.
6. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and about 2.5% hydrocortisone or hydrocortisone acetate formulated in a pharmaceutically-cosmetically acceptable vehicle.
7. A composition as in claim 1 or 2 comprising hydroquinone, retinoic acid, and an anti-inflammatory corticosteroid.

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